DETAILED ACTION

Claims 1-13 are currently pending in the instant application and are subject to the following new lack of unity requirement.

Election/Restrictions

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions, which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

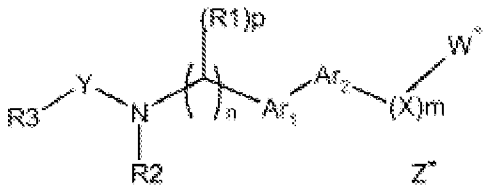
Claims 1-13 are drawn to more than one inventive concept (as defined in PCT Rule 13), and accordingly, a restriction is required according to the provision of PCT Rule 13.2

PCT Rule 13.2 states that the international application shall relate to one invention only or to a group of inventions so linked as to form a general inventive concept (requirement of unity of invention).

PCT Rule 13.2 states that unity of invention referred to in Rule 13.1 shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features *that makes a contribution over the prior art*.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I: Claims 1-5 drawn to a compound of formula (I),



. If this group is elected, applicants are requested to elect a single species for search purposes. For example, the compound of example 4 on page 20 of the specification.

Group II: Claims 6-13 drawn to a method of using a compound of formula (I). If this group is elected, applicants are requested to elect a single species and disorder for search purposes. For example, the compound of example 4 on page 20 of the specification, wherein the disorder is asthma as depicted in claim 8.

In the instant case, upon election of a single compound, the Office will review the claims and disclosure to determine the scope of the independent invention encompassing the elected compound (compounds which are so similar thereto as to be within the same inventive concept and reduction to practice). The scope of an independent invention will encompass all compounds within the scope of the claim, which fall into the same class and subclass as the elected compound, but may also include additional compounds, which fall in related subclasses. Examination will then proceed on the elected compound AND the entire scope of the invention encompassing the elected compound as defined by common classification. A clear statement of the examined invention, defined by those class(es) and subclass(es) will be set forth in the first action on the merits. Note that the restriction requirement will not be made final

until such time as applicant is informed of the full scope of compounds along with (if appropriate) the process of using or making said compound under examination.

The claims herein lack unity of invention under PCT rule 13.1 and 13.2 since, under 37 CFR 1.475(a) the compounds defined in the claims lack a significant structural element qualifying as the special technical feature that defines a contribution over the prior art. The technical feature of the instant claim(s) cannot be ascertained due to the numerous variables in the compound of claim 1.

Accordingly, unity of invention is considered to be lacking and restriction of the invention in accordance with the rules of unity of invention is considered to be proper. Additionally, the vastness of the claimed subject matter, and the complications in understanding the claimed subject matter imposes a serious burden on any examination of the claimed subject matter.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a invention to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected invention.**

The election of an invention may be made with or without traverse. To reserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the restriction requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after

the election, applicant must indicate which of these claims are readable on the elected invention.

If claims are added after the election, applicant must indicate which of these claims are readable upon the elected invention.

Should applicant traverse on the ground that the inventions are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the inventions to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

In addition, because of the plethora of classes and subclasses in each of the Inventions, a serious burden is imposed on the examiner to perform a complete search of the defined areas. Therefore, because of the reasons given above, the restriction set forth is proper and not to restrict would impose a serious burden in the examination of this application.

Advisory of Rejoinder

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and the product claims are subsequently found allowable, withdrawn process claims that depend from or otherwise require all the limitations of the allowable product claim will be considered for rejoinder. All claims directed a nonelected process invention must require all the limitations of an allowable product claim for that process invention to be rejoined.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103 and 112. Until all claims to the elected product are found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowable product claim will not be rejoined. See MPEP § 821.04(b). Additionally, in order to retain the right to rejoinder in accordance with the above policy, applicant is advised that the process claims should be amended during prosecution to require the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder**. Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

During a telephone conversation with Attorney Dara Dinner on 4/18/2011 a provisional election was made *without traverse* to prosecute the invention of Group I, comprising Claims 1-5 of Formula I depicted in claim 1. Further, an election of species was made of the compound depicted in Example 4 of the specification, page 20. Affirmation of this election must be made by applicant in replying to this Office action.

Priority

This application is a 371 of PCT/US05/07822, filed 03/11/2005, which claims benefit of 60/552,105, filed 03/11/2004.

Information Disclosure Statement

The information disclosure statement (IDS), filed on 2/27/2010 has been considered. Please refer to Applicant's copy of the 1449 submitted herewith.

Scope of the Elected Invention

Claims 1-13 are pending in this application. Claims 6-13 are withdrawn from further consideration by the examiner, 37 C.F.R. §1.142(b), as being drawn to a non-elected invention. The withdrawn subject matter is patentably distinct from the elected subject matter as it differs in structure and element and would require separate search considerations. In addition, a reference, which anticipates one group, would not render obvious the other.

The scope of the elected subject matter that will be examined and searched is as follows: Claims 1-5 drawn to a compound of formula (I) as depicted in claim 1, wherein

R3 is hetaryl;

Y is C(O);

Ar1 and Ar2 are phenyl;

X is C(R1)p;

R1 is hydrogen; and

W is a 6 or 7 membered ring system containing a quaternary ammonium nitrogen.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 and 5 are rejected under 35 U.S.C. 112, first paragraph, because the specification although enabling for a compound of Formula (I), wherein **W is piperazine, piperidine and diazepine with nitrogen as the point of attachment to the compound**, it is not enabled for all compounds of Formula (I), wherein **W** is a 6 or 7 membered ring system containing a quaternary ammonium nitrogen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

As stated in MPEP 2164.01(a), "there are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

The factors to be considered when determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, were described in In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) as:

1. the nature of the invention;
2. the breadth of the claims;
3. the state of the prior art;
4. the relative skill of those in the art;
5. the predictability or unpredictability of the art;
6. the amount of direction or guidance presented (by the inventor);

7. the presence or absence of working examples; and

8. the quantity of experimentation necessary (to make and/or use the invention).

The eight Wands factors are applied to Claims 1-3 and 5 of the present invention below:

(1) The Nature of the Invention

The nature of the invention is a diphenyl compound.

(2) The Breadth of the claims

The breadth of the claims encompass products wherein there is no support for wherein W is a 6 or 7 membered ring system containing a quaternary ammonium nitrogen. The applicable rule for interpreting the claims is that "each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description." See MPEP 2163(II)(1), citing In re Morris, 127 F.3d 1048, 1053-1054; 44 USPQ2d 1023, 1027 (Fed. Cir. 1997). In view of this rule, the products of Formula (I), wherein W is a 6 or 7 membered ring system containing a quaternary ammonium nitrogen may reasonably be interpreted to encompass an infinite number of combinations that involve a multitude of heterocyclic and non-heterocyclic compound compounds.

(3) The state of the prior art

Diphenyl compounds encompass a vast field. Specific support must be presented when a particular compound is being claimed. The processes of making

each compound is different as is the mechanism of action. Therefore, support is always given for claimed compounds.

(4) The relative skill of those in the art

The level of skill in the art (pharmaceutical chemists, physicians) would be high.

(5) The predictability or unpredictability of the art

The compounds claimed in the instant application, wherein the variables of the compound of Formula (I) are open to interpretation, include an extremely large scope of the potential products as encompassed by the claims rendering the prior art unpredictable for making or using the products as claimed on such a grand scale.

(6) The amount of direction or guidance presented (by the inventor)

The specification in the present invention discloses chemical examples of the species of Formula (I) found in the specification wherein W is piperidine, piperazine or diazepine only. The process of making the instantly claimed compounds with anything other than these compounds is unpredictable.

(7) The presence or absence of working examples

The specification provides guidance as to the W moiety, wherein W is piperdine, piperazine and diazepine only.

If additional examples than the one listed above, present please point them out.

(8) The quantity of experimentation necessary (to make and/or use the invention)

Given the absence of direction or guidance (or working examples) in the specification for any of the extremely large number of compounds that would be encompassed by the description W, it would cause a skilled artisan an undue amount of

experimentation to determine which product the process of making was describing. Also, a skilled artisan would not be able to predict if the instantly disclosed process would work in making those additional compounds. Therefore, to overcome this rejection, the scope of the compound should be defined to those compounds with support in the specification. For example, the compounds of formula (I), wherein **W is piperazine, piperidine or diazepine with nitrogen as the point of attachment to the compound**.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 5 is drawn to a pharmaceutical composition containing a compound of Claim 1 and further recites the intended use of the compounds. However, intended use is not a limitation of a compound. *In re Hack*, 114 PQ 161 (CCPA 1957). Therefore, Claim 5 is improper. By deleting the intended use language, i.e. “for the treatment of muscarinic acetylcholine receptor mediated diseases,” the rejection would be overcome.

Obviousness Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent

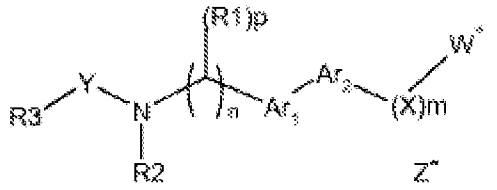
and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

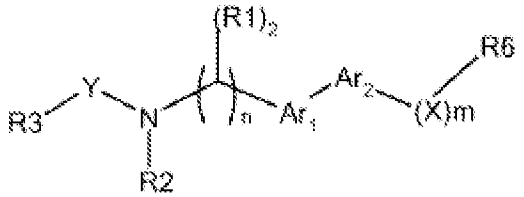
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-5 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-18, 20-23, 26, and 28-31 of US Pat. Pub. No. 2009/0253908 or USSN 10/598,743 (`743 App.) and 2009/0149447A1 or USSN 11/719,336 or US Pat No 7932247. The instant application and the `743 App were filed on the same day and a terminal disclaimer is required. The instant application is senior to the `247 Pat; however, a patent was issued on overlapping subject matter and a terminal disclaimer is required.

Instant claim 1 claims a compound of formula (I),



The `743 App. claims a compound of formula (I),



The difference between the copending application claims and the instant claims is that the instant claim contains a counter ion or a quaternary ammonium nitrogen at the W position, which corresponds to the R6 moiety of the copending application.

Although the conflicting claims are not identical, they are not patentably distinct from each other because one of ordinary skill in the art would recognize that the ionized species are obvious in view of copending compounds, which can be in pharmaceutical salt form and vice versa.

It is well known in the art that monatomic ions are formed by the addition of electrons to the valence shell of the atom, which is the outer-most electron shell in an atom, or the losing of electrons from this shell. The inner shells of an atom are filled with electrons that are tightly bound to the positively charged atomic nucleus, and so do not participate in this kind of chemical interaction. The process of gaining or losing electrons from a neutral atom or molecule is called ionization.

Applicants are claiming the Cl^- ion or Cl salt form of the compound of formula (I). See wherein the Z^- moiety is Cl^-. Ionization is commonly used in the pharmaceutical arts to obtain pharmaceutically acceptable salts.

Stahl teaches that "about half of all present-day drugs are used as salts, and for the chemist it is obvious to try improving the properties of a drug candidate by the formation of a suitable salt, in particular with the intention to enhance solubility and in consequence, the rate of dissolution as prerequisite parameters for absorption." See The Practice of Medicinal Chemistry, Second Edition, 2003, page 601.

Serjuddin teaches that the salt formation is common in the pharmaceutical arts and that the dissociation back and forth between the salt form and the free form is easy. See Advanced Drug Delivery Reviews, 59, 2007, pp. 603-616, esp. p. 603.

It is well known in the art that hydrochlorides are substantially more soluble than the free bases used to make them, so the hydrochloride typically improves the bioavailability. Further, hydrochlorides can be prepared in aqueous solution, in protic organic solvents, in aprotic organic solvents, and in non-polar solvents because hydrogen chloride can exist in both a covalent form in apolar solvents or as ionized protons and chloride ions in more polar solvents. The actual acidity varies being equal to the acidity of the conjugate acid of the solvent molecule. That is to say hydronium ions exist in water, protonated alcohol ions in alcohol, protonated acetic acid in glacial acetic acid or protonated ethyl acetate molecules in ethyl acetate. The multiple forms of HCl result in multiple techniques for the addition of the hydrogen and chloride ions to the pharmaceutical base we need to make into a salt.

Further, the utility of the instant compounds and the copending application are the same. Both compounds are muscarinic acetylcholine receptor antagonists and are used to treat a muscarinic acetylcholine receptor mediated disease, such as asthma.

In the absence of showing unobvious results, it would have been obvious to one of ordinary skill in the art at the time of the invention when faced with the prior filed applications that the instantly claimed compounds would be known.

The instant obviousness rejection is based on the close structural similarity of the instantly claimed compounds to the prior filed application compounds and the common utility shared among the compounds. There is an expectation among those of ordinary skill in the art that similar structural compounds will have similar properties and that modification of a known structure is mere experimentation within the means of a skilled artisan. See MPEP 2144.09(I). Therefore, claims 1-5 are rejected as obvious over the prior claims.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susannah Chung whose telephone number is (571) 272-6098. The examiner can normally be reached on M-F, 8am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on (571) 272-0699. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Susannah Chung/
Examiner, Art Unit 1626